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## Description

The present invention relates to a copolymer of lactic acid and glycolic acid, and a method for producing the copolymer in the absence of a catalyst.

5 In recent years, degradable polymers have attracted a good deal of attention, for example, as a readily degradable polymer serving to mitigate environmental pollution by plastics and also as a biodegradable polymer for medical uses.

As the method for producing a copolymer of lactic acid and glycolic acid, there is mentioned a method disclosed in U.S. Patent No. 4,273,920. In said U.S. Patent, it is stated that the copolymer being substantially  
10 free of polymerization catalyst is obtained by reacting lactic acid with glycolic acid in the presence of a readily removable strong acid ion-exchange resin, and removing the resin therefrom.

However, the copolymers produced by the above-described method all exhibit a dispersity in molecular weight as high as nearly 3 or more, and on the occasion of use, and give great complexity in factors involved in solubility and other aspects, thus being encountered with major problems in controlling  
15 such factors. Therefore, they cannot be said to be very favorable, when they are used, for example, as a biodegradable polymer for medical use. In addition, this method allows the strong acid ion-exchange resin being used as a polymerization catalyst to deteriorate due to heat during a polycondensation reaction under heating and to get dissolved in the resulting copolymer, thereby contributing to the development of coloration of the copolymer. Once the copolymer gets colored, furthermore, it is difficult to eliminate such  
20 coloration, and it is practically impossible to remove completely such coloration, and its coloration shows that the catalyst, i.e. strong acid ion-exchange resin, cannot be completely removed. It goes without saying that such coloration not only diminishes the value as an article of commerce but also is in the undesirable state, because it is attributed to impurities.

In view of such circumstances, the present inventors conducted repeatedly intensive research on the  
25 method for producing a copolymer of lactic acid and glycolic acid, which is effective and free from the above-mentioned disadvantages, and have found that the desired copolymer of lactic acid and glycolic acid is obtained by a polycondensation of these compounds in the absence of a catalyst. The present inventors conducted further research and have completed the present invention.

The present invention provides a copolymer of 50 to 95 weight % of lactic acid and 50 to 5 weight % of  
30 glycolic acid, which has a weight-average molecular weight of from 5,000 to 30,000 and a dispersity of from 1.5 to 2.

The invention also provides a method for producing a copolymer of lactic acid and glycolic acid as defined above, which comprises subjecting lactic acid and glycolic acid or a low molecular polymer or  
35 copolymer of them to a polycondensation reaction under heating at 150 to 250°C and reduced pressure of 3999.66 to 133.322 Pa (30 to 1 mm Hg) in the absence of a catalyst.

In the method of the present invention, lactic acid and glycolic acid are employed, as the starting materials, in the form of crystals, powders or granules as such, or in the form of an aqueous solution. The concentration of the solution is arbitrarily selected, preferably as high as possible, and more preferably not lower than 85% (w/w).

40 As the low molecular polymer of lactic acid or glycolic acid, there are mentioned an oligomer (e.g. dimer, trimer, etc.) of lactic acid, an oligomer (e.g. dimer, trimer, etc.) of glycolic acid and so on.

As the low molecular copolymer, employable in the present method as a starting material, of lactic acid and glycolic acid, there are mentioned one which is produced by subjecting lactic acid and/or glycolic acid to polycondensation reaction in the absence of a catalyst under for example about 100 to 150°C/46662.7 to  
45 3999.66 Pa (350 to 30 mmHg) for more than about 2 hours, normally about 2 to 10 hours, more preferably while increasing the temperature and the degree of reduced pressure stepwise from about 105°C/46662.7 Pa (350 mmHg) to 150°C/3999.66 Pa (30 mmHg) for about 5 to 6 hours, to thereby remove water. In this process, a low molecular polymer or copolymer of molecular weight of about 2000 to 4000 is obtained.

Furthermore, as the low molecular copolymers, there are mentioned ones which are obtainable by the  
50 manners described in Kogyo Kagaku Zasshi (Journal of the Chemical Society of Japan), vol. 68, pp. 983—986 (1965), i.e. lactic acid and glycolic acid is reacted in a normal atmospheric pressure and in the absence of a catalyst at 202°C for 6 hours, or U.S. Patent No. 2,362,511, i.e. lactic acid and glycolic acid is reacted at a temperature of 200°C holding the mixture at that temperature for a period of about 2 hours and subsequently continuing the heating for another period of about ½ hour under vacuum.

55 The ratio of lactic acid to glycolic acid in the present copolymer is preferably about 50 to 95 weight % of lactic acid and 50 to 5 weight % of glycolic acid, preferably about 60 to 95 weight % of lactic acid and about 40 to 5 weight % of glycolic acid, more preferably about 60 to 85 weight % of lactic acid and about 40 to 15 weight % of glycolic acid. The ratio is more preferably about 75±2 mole % of lactic acid and about 25±2 mole % of glycolic acid.

60 In the present method, a solvent may be employed, especially if starting materials are both crystals, powders or granules. As the solvent, there are mentioned, for example water, methanol, ethanol, acetone, etc.

The present method is carried out under heating and reduced pressure in the absence of a catalyst. The heating is carried out by heating the reaction system at about 150 to 250°C, preferably about 150 to 200°C.

65 The reduced pressure is normally about 3999.66 to 133.322 Pa (30 to 1 mmHg), preferably about 1333.22 to

133.322 Pa (10 to 1 mmHg). The reaction time of the present polycondensation reaction is normally about not less than 10 hours, preferably about 10 to 150 hours, more preferably about 10 to 100 hours.

Referring to the reaction steps and conditions in the present method when lactic acid and glycolic acid are employed as the starting materials, the following are preferably mentioned: A heating reaction under reduced pressure may be allowed to proceed at about 100 to 150°C/46662.7 to 3999.66 Pa (350 to 30 mmHg) for not less than about 2 hours, normally about 2 to 10 hours, for example, for about 5 to 6 hours while increasing the temperature and the degree of reduced pressure stepwise to about 105°C/46662.7 Pa (350 mmHg) to 150°C/3999.66 Pa (30 mmHg), to thereby remove water, followed by a dehydration polycondensation reaction at about 150 to 220°C/1333.22 to 133.322 Pa (10 to 1 mmHg) for not less than about 10 hours, and normally, up to about 100 hours may be adequate.

When the low molecular polymer or copolymer is employed as the starting material, preferable reaction conditions are as follows: A dehydration polycondensation reaction is carried out at about 150 to 200°C/1333.22 to 133.322 Pa (10 to 1 mmHg) for not less than 10 hours, and normally up to about 100 hours may be adequate.

After the termination of the reaction, the objective copolymer can be readily obtained by eliminating dusts through mere hot filtration of the reaction solution or filtration after dissolution of the copolymer in a suitable solvent such as methylene chloride, dichloroethane, chloroform, acetone in an amount of about equal to about 10-times that of the copolymer, whereupon no subsequent treatment is required to be carried out in the former case where the reaction solution is filtered as such and the employed solvent is concentrated or distilled off in the latter case where the reaction solution is filtered after being dissolved in a solvent. If desired, separation may be performed in accordance with the conventional method, for example, by pouring the filtered reaction solution, either directly or in the form of a concentrated filtrate in the case of a solvent being used, into a large amount of a precipitant, and if further required, purification may be carried out by reprecipitation, etc.

According to the present invention, there can be formed a copolymer consisting of lactic acid and glycolic acid units having a weight-average molecular weight of not less than about 5,000, preferably about 5,000 to 30,000, and the resulting copolymer has a dispersity of about 1.5 to 2.

As the copolymer obtained by the present method has a low degree of dispersity, and the distribution of the molecular weight of the copolymer is not wide.

Furthermore, in the present method, as no catalyst is used, the product is produced by polycondensation reaction in the absence of a catalyst, and is free of coloration.

The copolymer obtained by the present method can be utilized mainly as a base for drug preparation. For example, the copolymer can be advantageously utilized by incorporating steroid hormones, peptide hormones or anti-tumor agents, etc. into it to process into an embedded type or microcapsule type of controlled release preparations or by preparing fine particles containing an anti-tumor agent to process into a therapeutic agent for embolization.

The Experiment Examples and Examples are described below to illustrate the present invention in more detail.

#### Experiment Example 1

After 160 g (1.5 mol) of a 85% aqueous solution of lactic acid and 38 g (0.5 mol) of glycolic acid were mixed and heated under reduced pressure and under a nitrogen gas stream under the stepwise varying conditions of 100 to 150°C/46662.7 to 3999.66 Pa (350 to 30 mmHg) for 6 hours to remove the resulting water, the mixture was subjected to a dehydration polycondensation reaction at 175°C/666.61 Pa (5 mmHg) for 72 hours.

Shown in Table 1 is the relationship between reaction time and weight-average molecular weight attained in the production of copolymer of lactic acid and glycolic acid and its dispersity in accordance with the present process.

Also shown in Table 1 for the purpose of comparison are the results obtained with Dowex 50® (a cross-linked polystyrene resin, Dow Chemical Co., U.S.A.), a strongly acidic ion-exchange resin being commercially available, which was used as a polymerization catalyst.

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TABLE 1  
Comparison between the present process and process  
utilizing ion exchange resin in terms of molecular  
weight attained and its dispersity

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10	The present method			Control example (Dowex 50 used as a catalyst)	
	Reaction time	Weight-average mol. weight	Dispersity	Weight-average mol. weight	Dispersity
	12 hours	5,200	1.70	—	—
15	24 hours	9,600	1.68	9,100	2.43
	36 hours	13,500	1.71	11,400	2.63
	48 hours	15,800	1.66	14,900	2.80
20	60 hours	18,000	1.71	17,800	2.81
	72 hours	20,700	1.66	20,200	2.80
25	Appearance of the polymer*	White		Dark brown (The color deepens with time)	

30 Note: \*: Each of the copolymers obtained after the respective reaction time was dissolved in methylene chloride of the volume four times that of the copolymer, and the solution was filtered and then concentrated to distill off the solvent; the resulting copolymers were tested in accordance with JIS K8004—2 (namely, about 3 g of the test specimen is taken and examined on a sheet of white paper).

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The weight-average molecular weight and dispersity

$$40 \quad \text{dispersity} = \frac{\text{weight-average molecular weight}}{\text{number-average molecular weight}}$$

in the present specification were measured by gel permeation chromatography utilizing the standard polystyrene with the known molecular weight.

45 As is clear from Table 1, the present invention can permit readily the production of high-molecular-weight lactic acid-glycolic acid copolymers having a weight-average molecular weight of not less than about 5,000, whereby the resulting copolymers exhibit that colored appearance is hardly observed and show a dispersity of not more than 2.

50 Furthermore, analysis of nuclear magnetic resonance spectrometry on the resulting copolymer obtained in the above in a CDCl<sub>3</sub> solution indicates the following composition of lactic acid and glycolic acid.

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Reaction time	Copolymer ratio of the present copolymer	
	Copolymer ratio mol% (weight %)	
	Lactic acid	Glycolic acid
12 hours	75.5 (79.3)	24.5 (20.7)
24 hours	75.5 (79.3)	24.5 (20.7)
36 hours	75 (78.8)	25 (21.2)
48 hours	75.5 (79.3)	24.5 (20.7)
60 hours	76 (79.7)	24 (20.3)
72 hours	75.5 (79.3)	24.5 (20.7)

## Example 1

Weighed in a four-necked flask fitted with a thermometer, condenser and inlet tube for nitrogen gas were 191 g of a 85% aqueous solution of lactic acid and 17.5 g of glycolic acid, and heating under reduced pressure was carried out, under a stream of nitrogen gas, at the internal temperature and internal pressure of 105°C and 46662.7 Pa (350 mmHg) to 150°C and 3999.66 Pa (30 mmHg) over the period of 6 hours to remove the resulting water. Successively, heating was conducted under reduced pressure of 3 mmHg at the internal temperature of 175°C for 72 hours. The reaction solution was cooled to room temperature to give 140 g of an almost colorless bulk copolymer as a copolymer of lactic acid and glycolic acid. The copolymer showed a weight-average molecular weight of 22,000, a dispersity of 1.70 and a composition of lactic acid and glycolic acid of 89 mol %: 11 mol % (90.9 weight %: 9.1 weight %).

## Experiment Example 2

To 191 g of a 85% aqueous solution of lactic acid and 17.5 g of glycolic acid was added 6.8 g of Dowex 50W, and in the manner of Example 1, heating under reduced pressure was conducted, under a stream of nitrogen gas, at the internal temperature and internal pressure of 105°C and 46662.7 Pa (350 mmHg) to 150°C and 3999.66 Pa (30 mmHg), respectively, over the period of 6 hours to remove the resulting water. Furthermore, 6.8 g of Dowex 50W was additionally added, and heating was carried out under reduced pressure of 399.966 Pa (3 mmHg) at the internal temperature of 175°C for 72 hours. The reaction solution was filtered hot to remove the Dowex 50W, and the filtrate was cooled to room temperature to give 131 g of a bulk copolymer with a weight-average molecular weight of 23,700 and a dispersity of 2.88, which was brown colored. The resulting copolymer showed a composition of lactic acid and glycolic acid of 88.5 mol %: 11.5 mol % (90.5 weight %: 9.5 weight %).

## Example 2

Placed in the same polymerization apparatus as used in Example 1 were 106 g of a 85% aqueous solution of lactic acid and 76 g of glycolic acid, and heating under reduced pressure was carried out, under a stream of nitrogen gas, at the internal temperature and internal pressure of 105°C and 46662.7 Pa (350 mmHg) to 150°C and 3999.66 Pa (30 mmHg), stepwise, over the period of 3 hours and then the resulting water was removed. Successively, heating was conducted under reduced pressure of 399.966 Pa (3 mmHg) at the internal temperature of 180°C for 36 hours, and the reaction solution was cooled to room temperature to give 124 g of an almost colorless bulk polymer as a copolymer from lactic acid and glycolic acid. The copolymer showed a weight-average molecular weight of 15,300, a dispersity of 1.73, and a composition of lactic acid and glycolic acid of 50.5 mol %: 49.5 mol % (55.9 weight %: 44.1 weight %).

## Example 3

146 g of a 93% aqueous solution of lactic acid and 38 g of glycolic acid was used, a heating reaction was conducted at the temperature of 202°C for 6 hours, whereby a copolymer with a weight-average molecular weight of 2,700 and a composition of lactic acid and glycolic acid of 75 mol %: 25 mol % was obtained. Weighed in the same polymerization apparatus as used in Example 1 was 100 g of this

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copolymer, and heating was carried out under reduced pressure of 666.61 Pa (5 mmHg) at the internal temperature of 175°C for 70 hours, and the reaction solution was cooled to room temperature to give 92 g of an almost colorless bulk copolymer with a weight-average molecular weight of 17,700 and a dispersity of 1.85. The resulting copolymer showed a composition of lactic acid and glycolic acid of 75.5 mol %: 24.5 mol % (79.3 weight %: 20.7 weight %).

### Example 4

Placed in the same polymerization apparatus as used in Example 1 were 97 g of lactic acid dimer (Lactic acid lactate) and 54 g of glycolic acid dimer (Glycologlycolic acid), and heating was carried out under reduced pressure of 666.61 Pa (5 mmHg) at internal temperature of 180°C for 48 hours. The reaction solution was cooled to room temperature to give 105 g of an almost colorless bulk copolymer with a weight-average molecular weight of 18,300 and a dispersity of 1.76. The copolymer showed a composition of lactic acid and glycolic acid of 60 mol %: 40 mol % (65.1 weight %: 34.9 weight %).

### Example 5

After 3337 g (33 mol) of a 89% aqueous solution of lactic acid and 836 g (11 mol) of glycolic acid were mixed and heated under reduced pressure and under a nitrogen gas stream under the stepwise varying conditions of 100 to 150°C/46662.7 to 3999.66 Pa (350 to 30 mmHg) for 6 hours to remove the resulting water, the mixture was subjected to a dehydration polycondensation reaction at 175°C/666.61 Pa (5 mmHg) for 50 hours. The reaction solution was cooled to room temperature to give 2400 g of an almost colorless bulk copolymer with a weight-average molecular weight of 14400 and a dispersity of 1.66. The copolymer showed a composition of lactic acid and glycolic acid of 75 mol %: 25 mol % (78.8 weight %: 21.2 weight %).

### Claims (for Contracting States: BE, CH, DE, FR, GB, IT, LI, LU, NL, SE)

1. A copolymer of 50 to 95 weight % of lactic acid and 50 to 5 weight % of glycolic acid, which has a weight-average molecular weight of from 5,000 to 30,000 and a dispersity of from 1.5 to 2.
2. A copolymer as claimed in Claim 1, wherein the copolymer ratio is from 60 to 95 weight % of lactic acid and from 40 to 5 weight % of glycolic acid.
3. A copolymer as claimed in Claim 1, wherein the copolymer ratio is from 60 to 85 weight % of lactic acid and from 40 to 15 weight % of glycolic acid.
4. A copolymer as claimed in Claim 1, wherein the copolymer ratio is 75±2 mol % of lactic acid and 25±2 mol % of glycolic acid.
5. A method for producing a copolymer of lactic acid and glycolic acid as claimed in Claim 1, which comprises subjecting lactic acid and glycolic acid or a low molecular polymer or copolymer of them to a polycondensation reaction under heating at 150 to 250°C and reduced pressure of 3999.66 to 133.322 Pa (30 to 1 mmHg) in the absence of a catalyst.
6. A method as claimed in Claim 5, wherein the low molecular copolymer of lactic acid and glycolic acid is produced by subjecting lactic acid and glycolic acid to a condensation reaction in the absence of a catalyst and with removal of water, and the polycondensation reaction is carried out for not less than 10 hours.
7. A method as claimed in Claim 5, wherein the copolymer ratio is from 60 to 95 weight % of lactic acid and from 40 to 5 weight % of glycolic acid.
8. A method as claimed in Claim 5, wherein the copolymer ratio is from 60 to 85 weight % of lactic acid and from 40 to 15 weight % of glycolic acid.
9. A method as claimed in Claim 5, wherein the copolymer ratio is 75±2 mol % of lactic acid and 25±2 mol % of glycolic acid.

### Claims (for Contracting State: AT)

1. A method for producing a copolymer of 50 to 95 weight % of lactic acid and 50 to 5 weight % of glycolic acid, the copolymer having a weight-average molecular weight of from 5,000 to 30,000 and a dispersity of from 1.5 to 2, which comprises subjecting lactic acid and glycolic acid or a low molecular polymer or copolymer of them to a polycondensation reaction under heating at 150 to 250°C and reduced pressure of 3999.66 to 133.322 Pa (30 to 1 mmHg) in the absence of a catalyst.
2. A method as claimed in Claim 1, wherein the low molecular copolymer of lactic acid and glycolic acid is produced by subjecting lactic acid and glycolic acid to a condensation reaction in the absence of a catalyst and with removal of water, and the polycondensation reaction is carried out for not less than 10 hours.
3. A method as claimed in Claim 1, wherein the copolymer ratio is from 60 to 95 weight % of lactic acid and from 40 to 5 weight % of glycolic acid.
4. A method as claimed in Claim 1, wherein the copolymer ratio is from 60 to 85 weight % of lactic acid and from 40 to 15 weight % of glycolic acid.

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5. A method as claimed in Claim 1, wherein the copolymer ratio is  $75 \pm 2$  mol % of lactic acid and  $25 \pm 2$  mol % of glycolic acid.

### 5 Patentansprüche für die Vertragsstaaten BE CH DE FR GB IT LI LU NL SE:

1. Copolymer aus 50 bis 95 Gew.-% Milchsäure und 50 bis 5 Gew.-% Glycolsäure, das ein gewichtsmäßig durchschnittliches Molekulargewicht von 5.000 bis 30.000 und eine Dispersität von 1,5 bis 2 aufweist.
- 10 2. Copolymer nach Anspruch 1, worin das Copolymerverhältnis von 60 bis 95-Gew.-% Milchsäure und von 40 bis 5 Gew.-% Glycolsäure beträgt.
3. Copolymer nach Anspruch 1, worin das Copolymerverhältnis von 60 bis 85 Gew.-% Milchsäure und von 40 bis 15 Gew.-% Glycolsäure beträgt.
4. Copolymer nach Anspruch 1, worin das Copolymerverhältnis  $75 \pm 2$  Mol.-% Milchsäure und  $25 \pm 2$  Mol.-% Glycolsäure beträgt.
- 15 5. Verfahren zur Herstellung eines Copolymers aus Milchsäure und Glycolsäure nach Anspruch 1, das das Unterwerfen von Milchsäure und Glycolsäure oder eines Polymers oder Copolymers derselben mit niedrigem Molekulargewicht einer Polykondensationsreaktion unter Erwärmung auf 150 bis 250°C und bei vermindertem Druck von 3999.66 bis 133.322 Pa (30 bis 1 mm Hg) in Abwesenheit eines Katalysators umfaßt.
- 20 6. Verfahren nach Anspruch 5, worin das Copolymer von Milchsäure und Glycolsäure mit niedrigem Molekulargewicht hergestellt wird, indem Milchsäure und Glycolsäure einer Kondensationsreaktion in Abwesenheit eines Katalysators und unter Entfernung von Wasser unterworfen werden und die Polykondensationsreaktion innerhalb eines Zeitraums von nicht weniger als 10 Stunden durchgeführt wird.
- 25 7. Verfahren nach Anspruch 5, worin das Copolymerverhältnis von 60 bis 95 Gew.-% Milchsäure und von 40 bis 5 Gew.-% Glycolsäure beträgt.
8. Verfahren nach Anspruch 5, worin das Copolymerverhältnis von 60 bis 85 Gew.-% Milchsäure und von 40 bis 15 Gew.-% Glycolsäure beträgt.
9. Verfahren nach Anspruch 5, worin das Copolymerverhältnis  $75 \pm 2$  Mol.-% Milchsäure und  $25 \pm 2$  Mol.-% Glycolsäure beträgt.
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### Patentansprüche für den Vertragsstaat AT:

1. Verfahren zur Herstellung eines Copolymers aus 50 bis 95 Gew.-% Milchsäure und 50 bis 5 Gew.-% Glycolsäure, wobei das Copolymer ein gewichtsmäßig durchschnittliches Molekulargewicht von 5.000 bis 30.000 und eine Dispersität von 1,5 bis 2 aufweist, welches Verfahren das Unterwerfen von Milchsäure und Glycolsäure oder eines Polymers oder Copolymers derselben mit niedrigem Molekulargewicht einer Polykondensationsreaktion unter Erwärmen auf 150 bis 250°C und bei vermindertem Druck von 3999.66 bis 133.322 Pa (30 bis 1 mm Hg) in Abwesenheit eines Katalysators umfaßt.
- 35 2. Verfahren nach Anspruch 1, worin das Copolymer aus Milchsäure und Glycolsäure mit niedrigem Molekulargewicht hergestellt wird, indem Milchsäure und Glycolsäure einer Kondensationsreaktion in Abwesenheit eines Katalysators und unter Entfernung von Wasser unterworfen werden und die Polykondensationsreaktion innerhalb eines Zeitraums von nicht weniger als 10 Stunden durchgeführt wird.
- 40 3. Verfahren nach Anspruch 1, worin das Copolymerverhältnis von 60 bis 95 Gew.-% Milchsäure und von 40 bis 5 Gew.-% Glycolsäure beträgt.
- 45 4. Verfahren nach Anspruch 1, worin das Copolymerverhältnis von 60 bis 85 Gew.-% Milchsäure und von 40 bis 15 Gew.-% Glycolsäure beträgt.
5. Verfahren nach Anspruch 1, worin das Copolymerverhältnis  $75 \pm 2$  Mol.-% Milchsäure und  $25 \pm 2$  Mol.-% Glycolsäure beträgt.
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### Revendications pour les Etats Contractants BE CH DE FR GB IT LI LU NL SE:

1. Copolymère comprenant de 50 à 95% en poids d'acide lactique et de 50 à 5% en poids d'acide glyglycolique, ayant un poids moléculaire moyen de 5,000 à 30,000 et un degré de dispersion de 1,5 à 2.
- 55 2. Copolymère selon la revendication 1, dans lequel la proportion du copolymère est de 60 à 95% en poids d'acide lactique et de 40 à 5% en poids d'acide glycolique.
3. Copolymère selon la revendication 1, dans lequel la proportion du copolymère est de 60 à 85% en poids d'acide lactique et de 40 à 15% en poids d'acide glycolique.
4. Copolymère selon la revendication 1, dans lequel la proportion du copolymère est de  $75 \pm 2$  mole % d'acide lactique et de  $25 \pm 2$  mole % d'acide glycolique.
- 60 5. Procédé de préparation d'un copolymère d'acide lactique et d'acide glycolique selon la revendication 1, selon lequel on soumet de l'acide lactique et de l'acide glycolique ou un polymère ou copolymère de ceux-ci de faible poids moléculaire à une réaction de polycondensation en chauffant à 150 à 250°C et à une pression réduite à 3999,66 à 133,322 Pa (30 à 1 mm Hg) en l'absence d'un catalyseur.
- 65 6. Procédé selon la revendication 5, dans lequel le copolymère de faible poids moléculaire d'acide

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lactique et d'acide glycolique est préparé en soumettant de l'acide lactique et de l'acide glycolique à une réaction de condensation en l'absence d'un catalyseur et en éliminant l'eau, et la réaction de polycondensation est effectuée pendant une durée von inférieure à 10 heures.

7. Procédé selon la revendication 5, dans lequel la proportion du copolymère est de 60 à 96% en poids d'acide lactique et de 40 à 5% en poids d'acide glycolique.

8. Procédé selon la revendication 5, dans lequel la proportion du copolymère est de 60 à 85% en poids d'acide lactique et de 40 à 15% en poids d'acide glycolique.

9. Procédé selon la revendication 5, dans lequel la proportion du copolymère est de  $75 \pm 2$  mole % d'acide lactique et de  $25 \pm 2$  mole % d'acide glycolique.

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### Revendications pour l'Etat Contractant AT:

1. Procédé de production d'un copolymère comprenant de 50 à 95% en poids d'acide lactique et de 50 à 5% en poids d'acide glycolique, ce copolymère ayant un poids moléculaire moyen de 5 000 à 30 000 et un degré de dispersion de 1,5 à 2, selon lequel on soumet de l'acide lactique et de l'acide glycolique ou un polymère ou copolymère de ceux-ci de faible poids moléculaire à une réaction de polycondensation en chauffant à  $150$  à  $250^\circ\text{C}$  et à une pression réduite à  $3999,66$  à  $133,322$  Pa ( $30$  à  $1$  mm Hg) en l'absence d'un catalyseur.

2. Procédé selon la revendication 1, dans lequel le copolymère de faible poids moléculaire d'acide lactique et d'acide glycolique est préparé en soumettant de l'acide lactique et de l'acide glycolique à une réaction de condensation en l'absence d'un catalyseur et en éliminant l'eau, et la réaction de polycondensation est effectuée pendant une durée non inférieure à 10 heures.

3. Procédé selon la revendication 1, dans lequel la proportion du copolymère est de 60 à 95% en poids d'acide lactique et de 40 à 5% en poids d'acide glycolique.

4. Procédé selon la revendication 1, dans lequel la proportion du copolymère est de 60 à 85% en poids d'acide lactique et de 40 à 15% en poids d'acide glycolique.

5. Procédé selon la revendication 1, dans lequel la proportion du copolymère est de  $75 \pm 2$  mole % d'acide lactique et de  $25 \pm 2$  mole % d'acide glycolique.

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## Description

The present invention relates to use of a copolymer of lactic acid and glycolic acid in a controlled drug release preparation.

In recent years, degradable polymers have attracted a good deal of attention, for example, as a readily degradable polymer serving to mitigate environmental pollution by plastics and also as a biodegradable polymer for medical uses.

As the method for producing a copolymer of lactic acid and glycolic acid, there is mentioned a method disclosed in U.S. Patent No. 4,273,920. In said U.S. Patent, it is stated that the copolymer being substantially free of polymerization catalyst is obtained by reacting lactic acid with glycolic acid in the presence of a readily removable strong acid ion-exchange resin, and removing the resin therefrom.

However, the copolymers produced by the above-described method all exhibit a dispersity in molecular weight as high as nearly 3 or more, and on the occasion of use, and give great complexity in factors involved in solubility and other aspects, thus being encountered with major problems in controlling such factors. Therefore, they cannot be said to be very favorable, when they are used, for example, as a biodegradable polymer for medical use. In addition, this method allows the strong acid ion-exchange-resin being used as a polymerization catalyst to deteriorate due to heat during a polycondensation reaction under heating and to get dissolved in the resulting copolymer, thereby contributing to the development of coloration of the copolymer. Once the copolymer gets colored, furthermore, it is difficult to eliminate such coloration, and it is practically impossible to remove completely such coloration, and its coloration shows that the catalyst, i.e. strong acid ion-exchange resin, cannot be completely removed. It goes without saying that such coloration not only diminishes the value as an article of commerce but also is in the undesirable state, because it is attributed to impurities.

In view of such circumstances, the present inventors conducted repeatedly intensive research on the method for producing a copolymer of lactic acid and glycolic acid, which is effective and free from the above-mentioned disadvantages, and have found that the desired copolymer of lactic acid and glycolic acid is obtained by a polycondensation of these compounds in the absence of a catalyst. The present inventors conducted further research and have completed the present invention.

The present invention provides use of a copolymer to process into an embedded type or microcapsule type of controlled drug release preparation, wherein the copolymer is a copolymer of 50 to 95 weight % of lactic acid and 50 to 5 weight % of glycolic acid, - which has a weight-average molecular weight (measured by gel permeation chromatography) of from 5,000 to 30,000 and a dispersity of from 1.5 to 2, and which is free from catalyst residues.

The copolymer of lactic acid and glycolic acid can be produced by a method, which comprises subjecting lactic acid and glycolic acid or a low molecular polymer or copolymer of them to a polycondensation reaction in the absence of a catalyst under (1) a heating temperature of 150 to 250°C, (2) a reduced pressure of 1333.22 to 133.322 Pa (10 to 1 mmHg), and (3) a reaction time at said heating temperature and said reduced pressure of not less than 10 hours.

In the method, lactic acid and glycolic acid are employed, as the starting materials, in the form of crystals, powders or granules as such, or in the form of an aqueous solution. The concentration of the solution is arbitrarily selected, preferably as high as possible, and more preferably not lower than 85% (w/w).

As the low molecular polymer of lactic acid or glycolic acid, there are mentioned an oligomer (e.g. dimer, trimer, etc.) of lactic acid, an oligomer (e.g. dimer, trimer, etc.) of glycolic acid and so on.

As the low molecular copolymer, employable in the present method as a starting material, of lactic acid and glycolic acid, there are mentioned one which is produced by subjecting lactic acid and/or glycolic acid to polycondensation reaction in the absence of a catalyst under for example about 100 to 150°C/46662.7 to 3999.66 Pa (350 to 30 mmHg) for more than about 2 hours, normally about 2 to 10 hours, more preferably while increasing the temperature and the degree of reduced pressure stepwise from about 105°C/46662.7 Pa (350 mmHg) to 150°C/3999.66 Pa (30 mmHg) for about 5 to 6 hours, to thereby remove water. In this process, a low molecular polymer or copolymer of molecular weight of about 2000 to 4000 is obtained.

Furthermore, as the low molecular copolymers, there are mentioned ones which are obtainable by the manners described in Kogyo Kagaku Zasshi (Journal of the Chemical Society of Japan), vol. 68, pp. 983-986 (1965), i.e. lactic acid and glycolic acid is reacted in a normal atmospheric pressure and in the absence of a catalyst at 202°C for 6 hours, or U.S. Patent No. 2,362,511, i.e. lactic acid and glycolic acid is reacted at a temperature of 200°C holding the mixture at that temperature for a period of about 2 hours and subsequently continuing the heating for another period of about ½ hour under vacuum.

The ratio of lactic acid to glycolic acid in the present copolymer is preferably about 50 to 95 weight % of lactic acid and 50 to 5 weight % of glycolic acid, preferably about 60 to 95 weight % of lactic acid and about 40 to 5 weight % of glycolic acid, more preferably about 60 to 85 weight % of lactic acid and about 40 to 15

weight % of glycolic acid. The ratio is more preferably about 75±2 mole % of lactic acid and about 25±2 mole % of glycolic acid.

In the present method, a solvent may be employed, especially if starting materials are both crystals, powders or granules. As the solvent, there are mentioned, for example water, methanol, ethanol, acetone, etc.

The present method is carried out under heating and reduced pressure in the absence of a catalyst. The heating is carried out by heating the reaction system at about 150 to 250°C, preferably about 150 to 200°C. The reduced pressure is normally about 3999.66 to 133.322 Pa (30 to 1 mmHg), preferably about 1333.22 to 133.322 Pa (10 to 1 mmHg). The reaction time of the present polycondensation reaction is normally about not less than 10 hours, preferably about 10 to 150 hours, more preferably about 10 to 100 hours.

Referring to the reaction steps and conditions in the present method when lactic acid and glycolic acid are employed as the starting materials, the following are preferably mentioned: A heating reaction under reduced pressure may be allowed to proceed at about 100 to 150°C/46662.7 to 3999.66 Pa (350 to 30 mmHg) for not less than about 2 hours, normally about 2 to 10 hours, for example, for about 5 to 6 hours while increasing the temperature and the degree of reduced pressure stepwise to about 105°C/46662.7 Pa (350 mmHg) to 150°C/3999.66 Pa (30 mmHg), to thereby remove water, followed by a dehydration polycondensation reaction at about 150 to 220°C/1333.22 to 133.322 Pa (10 to 1 mmHg) for not less than about 10 hours, and normally, up to about 100 hours may be adequate.

When the low molecular polymer or copolymer is employed as the starting material, preferable reaction conditions are as follows: A dehydration polycondensation reaction is carried out at about 150 to 200°C/1333.22 to 133.322 Pa (10 to 1 mmHg) for not less than 10 hours, and normally up to about 100 hours may be adequate.

After the termination of the reaction, the objective copolymer can be readily obtained by eliminating dusts through mere hot filtration of the reaction solution or filtration after dissolution of the copolymer in a suitable solvent such as methylene chloride, dichloroethane, chloroform, acetone in an amount of about equal to about 10-times that of the copolymer, whereupon no subsequent treatment is required to be carried out in the former case where the reaction solution is filtered as such and the employed solvent is concentrated or distilled off in the latter case where the reaction solution is filtered after being dissolved in a solvent. If desired, separation may be performed in accordance with the conventional method, for example, by pouring the filtered reaction solution, either directly or in the form of a concentrated filtrate in the case of a solvent being used, into a large amount of a precipitant, and if further required, purification may be carried out by reprecipitation, etc.

According to the present method, there can be formed a copolymer consisting of lactic acid and glycolic acid units having a weight-average molecular weight of not less than about 5,000, preferably about 5,000 to 30,000, and the resulting copolymer has a dispersity of about 1.5 to 2.

As the copolymer obtained by the present method has a low degree of dispersity, and the distribution of the molecular weight of the copolymer is not wide.

Furthermore, in the present method, as no catalyst is used, the product is produced by polycondensation reaction in the absence of a catalyst, and is free of coloration.

The copolymer obtained by the present method can be utilized mainly as a base for drug preparation. For example, the copolymer can be advantageously utilized by incorporating steroid hormones, peptide hormones or anti-tumor agents, etc. into it to process into an embedded type or microcapsule type of controlled release preparations or by preparing fine particles containing an anti-tumor agent to process into a therapeutic agent for embolization.

The Experiment Examples and Examples are described below to illustrate the present invention in more detail.

#### Experiment Example 1

After 160 g (1.5 mol) of a 85% aqueous solution of lactic acid and 38 g (0.5 mol) of glycolic acid were mixed and heated under reduced pressure and under a nitrogen gas stream under the stepwise varying conditions of 100 to 150°C/46662.7 to 3999.66 Pa (350 to 30 mmHg) for 6 hours to remove the resulting water, the mixture was subjected to a dehydration polycondensation reaction at 175°C/666.61 Pa (5 mmHg) for 72 hours.

Shown in Table 1 is the relationship between reaction time and weight-average molecular weight attained in the production of copolymer of lactic acid and glycolic acid and its dispersity in accordance with the present process.

Also shown in Table 1 for the purpose of comparison are the results obtained with Dowex 50® (a cross-linked polystyrene resin, Dow Chemical Co., U.S.A.), a strongly acidic ion-exchange resin being commercially available, which was used as a polymerization catalyst.

TABLE 1  
Comparison between the present process and process  
utilizing ion exchange resin in terms of molecular  
weight attained and its dispersity

Reaction time	The present method		Control example (Dowex 50 used as a catalyst)	
	Weight-average mol. weight	Dispersity	Weight-average mol. weight	Dispersity
12 hours	5,200	1.70	—	—
24 hours	9,600	1.68	9,100	2.43
36 hours	13,500	1.71	11,400	2.63
48 hours	15,800	1.66	14,900	2.80
60 hours	18,000	1.71	17,800	2.81
72 hours	20,700	1.66	20,200	2.80
Appearance of the polymer*	White		Dark brown (The color deepens with time)	

Note: \*: Each of the copolymers obtained after the respective reaction time was dissolved in methylene chloride of the volume four times that of the copolymer, and the solution was filtered and then concentrated to distill off the solvent; the resulting copolymers were tested in accordance with JIS K8004—2 (namely, about 3 g of the test specimen is taken and examined on a sheet of white paper).

The weight-average molecular weight and dispersity

$$(\text{dispersity} = \frac{\text{weight-average molecular weight}}{\text{number-average molecular weight}})$$

in the present specification were measured by gel permeation chromatography utilizing the standard polystyrene with the known molecular weight.

As is clear from Table 1, the present invention can permit readily the production of high-molecular-weight lactic acid-glycolic acid copolymers having a weight-average molecular weight of not less than about 5,000, whereby the resulting copolymers exhibit that colored appearance is hardly observed and show a dispersity of not more than 2.

Furthermore, analysis of nuclear magnetic resonance spectrometry on the resulting copolymer obtained in the above in a  $\text{CDCl}_3$  solution indicates the following composition of lactic acid and glycolic acid.

Copolymer ratio of the present copolymer		
Reaction time	Copolymer ratio mol% (weight %)	
	Lactic acid	Glycolic acid
12 hours	75.5 (79.3)	24.5 (20.7)
24 hours	75.5 (79.3)	24.5 (20.7)
36 hours	75 (78.8)	25 (21.2)
48 hours	75.5 (79.3)	24.5 (20.7)
60 hours	76 (79.7)	24 (20.3)
72 hours	75.5 (79.3)	24.5 (20.7)

#### Example 1

Weighed in a four-necked flask fitted with a thermometer, condenser and inlet tube for nitrogen gas were 191 g of a 85% aqueous solution of lactic acid and 17.5 g of glycolic acid, and heating under reduced pressure was carried out, under a stream of nitrogen gas, at the internal temperature and internal pressure of 105°C and 46662.7 Pa (350 mmHg) to 150°C and 3999.66 Pa (30 mmHg) over the period of 6 hours to remove the resulting water. Successively, heating was conducted under reduced pressure of 3 mmHg at the internal temperature of 175°C for 72 hours. The reaction solution was cooled to room temperature to give 140 g of an almost colorless bulk copolymer as a copolymer of lactic acid and glycolic acid. The copolymer showed a weight-average molecular weight of 22,000, a dispersity of 1.70 and a composition of lactic acid and glycolic acid of 89 mol %: 11 mol % (90.9 weight %: 9.1 weight %).

#### Experiment Example 2

To 191 g of a 85% aqueous solution of lactic acid and 17.5 g of glycolic acid was added 6.8 g of Dowex 50W, and in the manner of Example 1, heating under reduced pressure was conducted, under a stream of nitrogen gas, at the internal temperature and internal pressure of 105°C and 46662.7 Pa (350 mmHg) to 150°C and 3999.66 Pa (30 mmHg), respectively, over the period of 6 hours to remove the resulting water. Furthermore, 6.8 g of Dowex 50W was additionally added, and heating was carried out under reduced pressure of 399.966 Pa (3 mmHg) at the internal temperature of 175°C for 72 hours. The reaction solution was filtered hot to remove the Dowex 50W, and the filtrate was cooled to room temperature to give 131 g of a bulk copolymer with a weight-average molecular weight of 23,700 and a dispersity of 2.88, which was brown colored. The resulting copolymer showed a composition of lactic acid and glycolic acid of 88.5 mol %: 11.5 mol % (90.5 weight %: 9.5 weight %).

#### Example 2

Placed in the same polymerization apparatus as used in Example 1 were 106 g of a 85% aqueous solution of lactic acid and 76 g of glycolic acid, and heating under reduced pressure was carried out, under a stream of nitrogen gas, at the internal temperature and internal pressure of 105°C and 46662.7 Pa (350 mmHg) to 150°C and 3999.66 Pa (30 mmHg), stepwise, over the period of 3 hours and then the resulting water was removed. Successively, heating was conducted under reduced pressure of 399.966 Pa (3 mmHg) at the internal temperature of 180°C for 36 hours, and the reaction solution was cooled to room temperature to give 124 g of an almost colorless bulk polymer as a copolymer from lactic acid and glycolic acid. The copolymer showed a weight-average molecular weight of 15,300, a dispersity of 1.73, and a composition of lactic acid and glycolic

acid of 50.5 mol %: 49.5 mol % (55.9 weight %: 44.1 weight %).

#### Example 3

5 146 g of a 93% aqueous solution of lactic acid and 38 g of glycolic acid was used, a heating reaction was conducted at the temperature of 202°C for 6 hours, whereby a copolymer with a weight-average molecular weight of 2,700 and a composition of lactic acid and glycolic acid of 75 mol %: 25 mol % was obtained. Weighed in the same polymerization apparatus as used in Example 1 was 100 g of this copolymer, and heating was carried out under reduced pressure of 666.61 Pa (5 mmHg) at the internal temperature of 175°C for 70 hours, 10 and the reaction solution was cooled to room temperature to give 92 g of an almost colorless bulk copolymer with a weight-average molecular weight of 17,700 and a dispersity of 1.85. The resulting copolymer showed a composition of lactic acid and glycolic acid of 75.5 mol %: 24.5 mol % (79.3 weight %: 20.7 weight %).

#### Example 4

15 Placed in the same polymerization apparatus as used in Example 1 were 97 g of lactic acid dimer (Lactic acid lactate) and 54 g of glycolic acid dimer (Glycologlycolic acid), and heating was carried out under reduced pressure of 666.61 Pa (5 mmHg) at internal temperature of 180°C for 48 hours. The reaction solution was cooled to room temperature to give 105 g of an almost colorless bulk copolymer with a weight-average molecular weight of 18,300 and a dispersity of 1.76. The copolymer showed a composition of lactic acid and glycolic acid of 60 mol %: 40 mol % (65.1 weight %: 34.9 weight %). 20

#### Example 5

25 After 3337 g (33 mol) of a 89% aqueous solution of lactic acid and 836 g (11 mol) of glycolic acid were mixed and heated under reduced pressure and under a nitrogen gas stream under the stepwise varying conditions of 100 to 150°C/46662.7 to 3999.66 Pa (350 to 30 mmHg) for 6 hours to remove the resulting water, the mixture was subjected to a dehydration polycondensation reaction at 175°C/666.61 Pa (5 mmHg) for 50 hours. The reaction solution was cooled to room temperature to give 2400 g of an almost colorless bulk copolymer with a weight-average molecular weight of 14400 and a dispersity of 1.66. The copolymer showed a composition of lactic acid and glycolic acid of 75 mol %: 25 mol % (78.8 weight %: 21.2 weight %). 30

#### Claims

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1. Use of a copolymer to process into an embedded type or microcapsule type of controlled drug release preparation, wherein the copolymer is a copolymer of 50 to 95 weight % of lactic acid and 5 to 5 weight % of glycolic acid, which has a weight-average molecular weight (measured by gel permeation chromatography) of from 5,000 to 30,000 and a dispersity of from 1.5 to 2, and which is free from catalyst residues. 40
  2. Use as claimed in Claim 1, wherein the copolymer ratio is from 60 to 95 weight % of lactic acid and from 40 to 5 weight % of glycolic acid.
  - 45 3. Use as claimed in Claim 1, wherein the copolymer ratio is from 60 to 85 weight % of lactic acid and from 40 to 15 weight % of glycolic acid.
  4. Use as claimed in Claim 1, wherein the copolymer ratio is 75±2 mol % of lactic acid and 25±2 mol % of glycolic acid.
  - 50 5. Use as claimed in Claim 1, wherein a steroid hormone, peptide hormone or anti-tumor agent is incorporated into the preparation.

#### Patentansprüche

- 55
1. Verwendung eines Copolymers zur Verarbeitung zu einem Präparat mit gesteuerter Arzneimittelfreisetzung vom Einbettungs- oder Mikrokapseltyp, worin das Copolymer ein Copolymer von 50 bis 95 Gew.-%

Milchsäure und 50 bis 5 Gew.-% Glykolsäure ist, das ein Gewichtschnitts-Molekulargewicht (gemessen durch Gelpermeationschromatographie) von 5.000 bis 30.000 und eine Dispersität von 1,5 bis 2 aufweist sowie frei von Katalysatorresten ist.

- 5 2. Verwendung nach Anspruch 1, worin das Copolymerverhältnis 60 bis 95 Gew.-% Milchsäure und 40 bis 5 Gew.-% Glykolsäure beträgt.
3. Verwendung nach Anspruch 1, worin das Copolymerverhältnis 60 bis 85 Gew.-% Milchsäure und 40 bis 15 Gew.-% Glykolsäure beträgt.
- 10 4. Verwendung nach Anspruch 1, worin das Copolymerverhältnis 75±2 Mol-% Milchsäure und 25±2% Glykolsäure beträgt.
5. Verwendung nach Anspruch 1, wobei ein Steroidhormon, Peptidhormon oder Antitumorwirkstoff in das Präparat eingearbeitet wird.

#### Revendications

- 20 1. Utilisation d'un copolymère dans la fabrication d'un médicament à libération prolongée du genre enrobé ou du genre microcapsule, dans laquelle le copolymère est un copolymère de 50 à 95% en poids d'acide lactique et de 50 à 5% en poids d'acide glycolique, ayant un poids moléculaire moyen (mesuré par chromatographie de perméation sur gel) de 5 000 à 30 000 et un degré de dispersion de 1,5 à 2 et qui est exempt de résidus de catalyseur.
- 25 2. Utilisation selon la revendication 1, dans laquelle la proportion du copolymère est de 60 à 95% en poids d'acide lactique et de 40 à 5% en poids d'acide glycolique.
3. Utilisation selon la revendication 1, dans laquelle la proportion du copolymère est de 60 à 85% en poids d'acide lactique et de 40 à 15% en poids d'acide glycolique.
- 30 4. Utilisation selon la revendication 1, dans laquelle la proportion du copolymère est de 75±2 mole % d'acide lactique et de 25±2 mole % d'acide glycolique.
5. Utilisation selon la revendication 1, dans laquelle une hormone stéroïde, une hormone peptidique ou un agent antitumoral est incorporé dans le médicament.

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